

C. K. Ingold. A chemical revolutionary

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Abstract: The development of Ingold's treatments of chemical structure and reactivity, and his work as a teacher, are discussed together with some personal recollections.

It is difficult for anyone closely involved with Christopher Ingold to write dispassionately about him. He was the most remarkable man that I have known and I owe a great deal to him. My comments are subjective and based on personal recollections tempered by hindsight. As a result I rely less on references to published work than is usual.

Ingold's scientific career began at a time when Organic Chemistry had come of age. The concepts of structure and chemical bonding were established and major progress had been made in the structural elucidation and synthesis of relatively complex organic compounds. The discovery of the electron and the development of quantum mechanics opened the way for quantitative treatments of structure and reactivity. At the same time new experimental methods were providing information on the size and shape of organic molecules.

A summary of Ingold's scientific career is given in a very warm and generous biographical memoir by C.W.Shoppee (1) who had worked with Ingold at the University of Leeds. Ingold's research career began in 1913 with J.F.Thorpe at Imperial College, followed by a brief interlude in industrial chemistry (1918-1920) and then a lectureship at Imperial College (1920-1924). In 1924 he went to the University of Leeds as Professor of Organic Chemistry and in 1930 returned to London as Professor of Chemistry at University College. In 1937 Ingold became Head of the department as Director of the Laboratories and on retirement from this position in 1961 he remained as Professor Emeritus and Special Lecturer until his death in 1970.

Thorpe had worked with Perkin, so Ingold was linked to the heroic age of Organic Chemistry. The first publication in 1915 was on spiro-compounds (2), reflecting Thorpe's interest in cyclisation. The last research publication was on the mechanism of electrophilic substitution at a saturated carbon atom (3), and was followed by the second edition of Ingold's monumental monograph (4) which was No.443 and the last of his publications. In collaboration with Thorpe bulky gem-dialkyl substituents were shown to assist cyclisation, and the so called Thorpe-Ingold effect continues to be of mechanistic interest in applications of molecular modelling to problems of organic reactivity in cyclisations.

The revolution in Organic Chemistry which took place during Ingold's scientific lifetime would have taken place without him, but would have taken a different form. The original Kekulé-Couper descriptions of bonding fitted uncomfortably with the properties of conjugated systems, including benzenoid compounds, and several authors were discussing the role of polar groups in terms of alternating effects along a carbon chain. These descriptions led to the concept of the transmission of electronic effects along conjugated systems. In some cases these ideas were used as ad hoc rationalisations of the results of

product studies and in the development of preparative methods. Ingold's genius allowed him to bring together the concepts of electronic effects which he classified as inductive and mesomeric. (The term "mesomeric", although descriptively useful, has largely been displaced by "resonance" although its derivation is less obvious to organic chemists). Ingold also saw the interplay of steric and electronic effects and their separation was a major and long term goal of his scientific work.

Postulation of the existence of electronic and steric effects on structure and reactivity was necessary, but not sufficient, and the Ingold approach relied massively on the development of quantitative experimental methods. This area had been the domain of physical chemists, but Ingold cared little for these arbitrary classifications in a subject which he saw as a whole. Solving any problem involved the development of ideas, the testing of these ideas by every conceivable method, followed by a grand synthesis. The unavailability of equipment was not allowed to stand in the way, although the full implementation of this approach had to wait until Ingold's move to University College.

Shoppee gives a detailed classification of Ingold's publications by subject, which is especially useful in illustrating how ideas developed and how Ingold pursued particular interests throughout much of his scientific career (1). Ingold's academic appointments were in only three institutions, so I have selected topics illustrating how his interests expanded with time.

Imperial College Period: cyclisation; Thorpe-Ingold effect; ring conformations; tautomerism; the benzene nucleus.

Leeds Period: directive substituent effects; theories of electronic effects; acid dissociation; carboxylic ester hydrolysis; elimination and addition reactions; tautomerism and mesomerism; rearrangements.

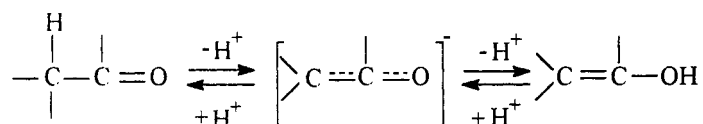
University College Period: duality of mechanisms of substitution and elimination; mechanistic classification of ester hydrolysis; separation of steric and electronic effects; solvent effects and mechanism; relative configurations and the Walden inversion; applications of stable and radioactive isotopes to kinetics and bond cleavage; nitration and nitrosation at carbon, nitrogen and oxygen centres; the nitronium ion; aromatic and aliphatic rearrangements; spectroscopic treatments of ground and excited states; substitution in octahedral complexes; electrophilic substitution at alkyl centres.

Instrumental methods available when Ingold started his work were very limited and most instruments were manually operated, so collection of data required time, patience and at least a modicum of skill. Reactions were followed by chemical analysis or, where feasible, polarimetrically, colourimetrically, electrochemically or dilatometrically. Electronic spectra were obtained visually, with the risk of eye damage (1), or photographically, and ir spectra required point by point measurement. The Underground railway was so close to the University College laboratories that ir spectra were obtained late at night after the Underground closed. As a result of these constraints one tried to obtain as much information as possible from a given experiment.

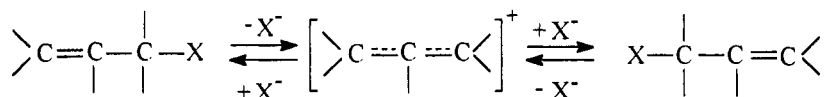
Ingold was far ahead of his time in seeing how isotopes were the key to solving many problems. Comparison of rates of racemisation and halide-ion isotopic exchange solved the problem of the Walden inversion and the establishment of relative configurations. Deuterium labelling of benzene and acetylene was a crucial part of Ingold's spectroscopic work on ground and electronically excited states and is discussed later. A serious problem was that neither the isotopes nor the measuring equipment were readily available and a major effort was devoted to preparation of radioactive and enrichment of stable isotopes and construction of the apparatus needed for their measurement.

I have arbitrarily selected some topics which I feel demonstrate Ingold's scientific versatility and his ability to move beyond the perceived boundaries of organic chemistry.

1. Lapworth's classical bromination experiment had demonstrated the slow conversion of a ketone into an enol. Ingold introduced the concept of the mesomeric anion and subsequently established the identity of rates of racemisation, bromination and hydrogen exchange (5).

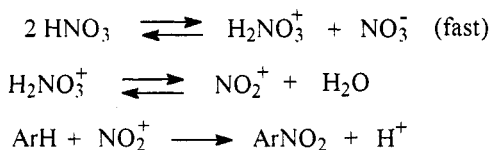


An analogous approach was applied to allylic rearrangements (5).



The concepts of the mesomeric ion, and kinetic and thermodynamic control of products, were applied to these problems. Ingold was also especially careful in drawing distinctions between intermediates and transition states and applied principles that later became known as the Hammond Postulate.

2. Nitration in organic solvents (nitromethane or acetic acid) with HNO_3 in large excess over the aromatic substrate, ArH , was zero order in $[\text{ArH}]$ for relatively reactive arenes, but first order in $[\text{ArH}]$ for unreactive arenes. Ingold was especially careful in distinguishing between reaction order, an experimentally observable property, and molecularity which had to be established. Reaction was inhibited by NO_3^- (and by nitrogen oxides which generate NO_3^-). The kinetic forms were elegantly explained in terms of the following reactions (6).

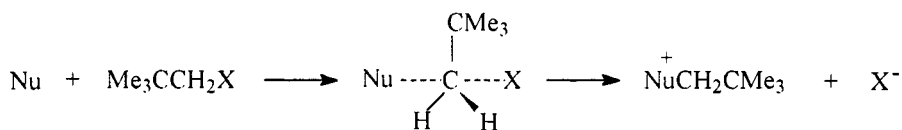


Subsequently rates of oxygen exchange and nitration were related in $\text{HNO}_3\text{-H}_2^{18}\text{O}$ (7) and nitration at oxygen centres was examined kinetically (6).

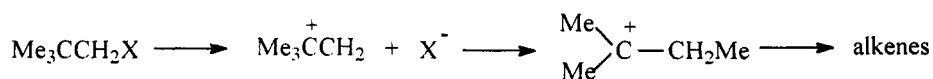
This kinetic evidence for nitration with NO_2^+ was complemented by isolation of its salts and spectroscopic evidence for its existence as a linear triatomic species (6).

3. Ingold's willingness and ability to move into new fields outside the accepted limits of Organic Chemistry are well illustrated by his spectroscopic work on conformations of ground and electronically excited states where he made extensive use of deuterium labelling to change frequencies without changing force constants. He had a long-standing interest in benzene and recognised the potential of molecular (Raman and ir) spectroscopy in the study of the ground state and of electronic absorbance in examining the electronically excited state (8). Demonstration of the bent structure of electronically excited acetylene was the first example of this type of study (9).

4. Neopentyl halides (10) were known to be much less reactive than simple primary alkyl halides in $\text{S}_{\text{N}}2$ reactions with nucleophiles because, regardless of conformation, there is intense interference between β -methyl and the entering or leaving groups.



However, these halides are not unusually unreactive under $\text{S}_{\text{N}}1$ conditions in moist formic acid, but here generation of a carbocation leads to rearranged products via a Wagner-Meerwein rearrangement.



The work was extended to a comprehensive investigation of steric effects on rates of halide ion exchange, followed isotopically or by the Finkelstein reaction. Hydrogen was systematically replaced by CH_3 in the following series:

α -series: CH_3 ; CH_3CH_2 ; $(\text{CH}_3)_2\text{CH}$; $(\text{CH}_3)_3\text{C}$

β -series: CH_3CH_2 ; $\text{CH}_3\text{CH}_2\text{CH}_2$; $(\text{CH}_3)_2\text{CHCH}_2$; $(\text{CH}_3)_3\text{CCH}_2$.

Incremental activation entropies and enthalpies for the two series were computed from consideration of non-bonding interactions in the initial and transition states, based on bond lengths and angles, force constants and compressibilities. This excursion into what has become known as molecular mechanics was carried out with Ingold's mathematical ability and a mechanical calculator, which was the only available instrument 40 years ago (10). In this study comparisons of theory with experiment were clouded by problems in determination of second order rate constants of substitution in the *t*-butyl halides where elimination and subsequent addition made a larger contribution to the overall reaction than had been assumed. These experimental errors do not detract from the boldness of this approach or the brilliance of the treatment.

Ingold loved to develop new scientific terms and many of them, e.g. nucleophilic and electrophilic, $\text{S}_{\text{N}}1$ and $\text{S}_{\text{N}}2$, are so widely used, even in elementary texts, that their provenance has been forgotten. He was careful not to mix Latin and Greek roots and paid great attention to the derivation of the new terms. But he sometimes took a cavalier view of nomenclature. His choice of "carbonium ion" for a trivalent carbocation was probably not one of his best selections and, for reasons which he could not foresee, has become a source of confusion. However, his development, with Cahn and Prelog, of the R and S stereochemical system (11) cleared away major ambiguities and the priority definitions have proved to be very useful in other aspects of isomerism.

There were occasional scientific errors, but surprisingly few in view of the extent and breadth of Ingold's scientific work. For example, some of the kinetic data on octahedral substitution were misinterpreted (12), although Ingold's incursion into this field stimulated extensive and continuing interest. There were questions regarding the interpretation of salt effects on aliphatic nucleophilic substitution in solvents of very low polarity (10,13). The great convenience of the "curved-arrow" system of electronic bookkeeping has had the unfortunate effect of leading some to believe that electrons move in pairs and created an unnecessary dichotomy between "heterolytic" and "homolytic" processes. So far as I can judge neither Hughes nor Ingold recognised the significance of the evidence of Kornblum and others on nucleophilic aliphatic substitutions involving electron transfer (14).

Ingold believed that he could write "Finis" to a problem and that was his goal. Some problems, such as determination of a structure by X-ray crystallography, or completion of a synthesis, are amenable to this approach. But in mechanistic work on solution reactions new ideas and new experimental methods will require new interpretations, so we never reach the horizon, or the end of the rainbow.

In discussing the formation of carbocationic intermediates Ingold gave especial emphasis to the importance of solvation, but could only discuss it qualitatively (10). Now, with the availability of computational methods, it is possible to include solvent molecules in the modelling of structures of initial and transition states. Experimental methods are throwing new light on the mechanism of the final step of nitration, *viz.*, attack of the nitronium ion upon arenes (15). Valence-bond treatments are illustrating the factors that control nucleophilicity (16). However, all these advances are based on the intellectual scaffolding which Ingold erected in developing treatments of reaction mechanisms.

What of Ingold the teacher? The present day gurus who pontificate about "good teaching" would have been appalled by Ingold's approach. His teaching aids were chalk, chalkboard and an incisive mind. When he started his advanced course he told us that he assumed that we understood basic organic chemistry: There would be no concessions to our ignorance and if we did not know the background material we should immediately read the appropriate text-book. But his classroom lectures were elegant intellectual

presentations which forced his audience to think, and keep on thinking, and after class he displayed infinite patience in dealing with questions.

His teaching went far beyond the classroom. In both the first and second edition of his monograph chapters are prefaced with historical introductions illustrating the developments which led to comprehensive treatments of structure and mechanism (4). Such introductions are inevitably lacking in more recent texts, but Ingold's early experience allowed him, in the late 1960's, to discuss, with authority, ideas that had developed over a hundred years, from the foundations of the subject.

Ingold had little regard for the division of chemistry into subdisciplines, because he saw the subject as a whole and as part of the grand pattern of science. As a result Chemistry at University College was not separated into the arbitrary, historically-based, divisions of Organic, Inorganic and Physical Chemistry, although members of department had their own interests and expertise. I suspect that Ingold would not have regarded himself as a "Physical Organic" chemist and I think would have objected to the qualification. To this extent he differed from L.P.Hammett who entered the subject as a physical chemist, and regarded himself as such. Ingold's view of science as a whole was exemplified by his role in the development of a new B.Sc. degree after World War II, which involved extensive grounding in the sciences contiguous to Chemistry.

Ingold was in great demand as a speaker and, especially in visits abroad, he illustrated and expanded on the new ideas in Chemistry (1). These visits had long term effects, both scientific and in the development of personal relationships. His close interaction with the Mangini group at the University of Bologna was largely responsible for the present deep interest in quantitative organic chemistry in Italy, and similar contacts were important around the world.

Ingold was intellectually patient and generous, although not to those of his scientific opponents who he felt were careless in their experimental work or interpretation. An incident, told to me by Professor Robert Moss, illustrates Ingold's generous manner. Moss, then an Assistant Professor, had examined the stereochemistry of amine deaminations by nitrous acid, and his results apparently disagreed with those published earlier by Hughes and Ingold. Correspondence with Ingold, and subsequent discussions at an international meeting, established the source of the discrepancy. The amines examined by Moss differed from those studied earlier because they self-associated to form micelles which controlled the direction of reagent attack and therefore of the stereochemistry, providing an early example of this control mechanism (17).

The scientific community has an honourable record in assisting victims of political persecution and Ingold helped to find havens for scientists fleeing from Nazi Germany, and subsequently from Communist countries, and he frequently helped foreign students financially from his own pocket. He removed his name from many papers covering work that he had directed or inspired, especially when the authors were junior colleagues who were making their way in the scientific world.

It is very difficult to separate Ingold the scientist from Ingold the individual because of his overwhelming devotion to science. He tackled problems by the total immersion method of closing himself off and giving total attention to the scientific conundrum at hand until it was solved to his satisfaction. During his scientific career Ingold had extensive responsibilities as head of an expanding department and, for some of the time, as Vice Provost of the College. There were also extensive outside duties to scientific organizations, nationally and internationally. His close collaborator, E.D.Hughes played a crucial role during this time, not only scientifically, but also administratively within the department, and as the department grew in the 1950's new and independent areas developed.

I should also mention some personal recollections. While at Leeds Ingold had taken up rock climbing on short, but very steep, escarpments in the Yorkshire hills, and later I climbed with him and his son, Keith, and daughter, Dilys. He greatly enjoyed mountaineering, as well as bird-watching, a passion which I did not share. But there was never enough time to do the worthwhile things. He once lamented on this question on the top of a Welsh mountain, then added the qualification that climbing was one of the worthwhile things. He kept a model of the Matterhorn on his desk and one of his regrets was that he had not climbed this mountain.

In 1965 Ingold received the first Flack Norris Award of the American Chemical Society and after the meeting he, T.C.Bruice, and I, visited his son, Keith, in Ottawa. Keith lived by the Rideau River so water-skiing was in order, and Ingold, then 71, but regarding age as no deterrent, was determined to water-ski. Water-skiing is a problem in dynamics rather than statics, and Keith's boat did not have quite the power to make the transition fast enough, so it was not easy to get the necessary lift from the skis. In much the same way in the late 1950's Ingold decided to see the Sahara, so he drove from England to Gibraltar, took the ferry and headed into the desert.

Science is a cooperative, but competitive, enterprise, and participants play different roles. Many chemists recognized early in this century that developments, experimental and theoretical, in physics would have a profound effect on the understanding of organic structure and mechanism. This view was not universal, and many organic chemists resisted the introduction of physical principles into the subject. But, as so often happens, with time heresies become orthodoxies, and Ingold's comprehensive treatments became the basis not only for teaching, but also in research on preparative methods, and their provenance is, for the most part, forgotten. Synthetic chemists are now so comfortable with these ideas that they are liable to use them uncritically, and, what is worse, feel that all that one needs to know is known about the details of chemical reactivity in solution. This view is no more likely to be correct now than it was in 1913 when Ingold began his career as a research scientist.

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